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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/642,492
Filing Date: August 18, 2000
Appellant(s): VAN NEST ET AL.

Jill A. Jacobson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 06, 2006 appealing from the Office action mailed June 13, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejection of claims 1, 13-23, 25-30, 32-33 and 37-42 under 35 U.S.C. § 112, 1st paragraph, scope of enablement is withdrawn.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 98/55495	Schwartz et al.	12-1998
WO 98/16247	Carlson et al.	4-1998
4673574	Anderson et al.	6-1987

Chu et al. CpG Oligonucleotides act as adjuvants that switch on T helper 1 (Th1) immunity. J. Exp. Med., November 17, 1997, Vol. 186, No. 10, 1623-1631.

Durali et al. Cross reactions between the cytotoxic T-lymphocyte responses of human immunodeficiency virus-infected African and European patients. Journal of Virology, May 1998, Vol. 72, No. 5, 3547-3553.

Horner et al. Immunostimulatory DNA is a Potent Mucosal Adjuvant. Cellular Immunology, November 1998, Vol. 190, No. 1, 77-82.

Lee et al. Control immune responses by gene immunization. Ann. Med., 1998, Vol. 30, 460-468.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al.[1], as further evidenced by Horner et al.[2] or Chu et al.[3]

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[1] Schwartz et al. WO 98/55495, published December 1998.
[2] Horner et al. Immunostimulatory DNA is a Potent Mucosal Adjuvant. Cellular Immunology, November 1998, Vol. 190, No. 1, 77-82.

The claims are directed to method comprising the active step(s) of co-administering to an individual i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and ii) a second antigen, wherein the immunomodulatory polynucleotide comprises the sequence 5'-cytosine,guanine-3', the CpG motif. The claims also contain language directing the practice of the method to modulate an immune response to the second antigen in the individual.

Claim 13, which depends on claim 1, limits the first antigen to be an allergen. Claim 41, which depends on claim 13, limits the allergen to Amb. Claim 14, which depends on claim 1, limits the first antigen to be a conserved polypeptide of a virus. Claim 17, which depends on claim 1, requires the first antigen to be a carrier molecule. Claim 20, which depends on claim 1, requires the first antigen to be associated with a carrier molecule. Claim 21, which depends on claim 1, specifies that the immune response be modulated by stimulating a Th1 response to the second antigen. Claims 22-23, which depend on claim 21, require the production of a second antigen-specific Th1-associated antibodies be stimulated and the production of interferon gamma be stimulated, respectively. Claim 25, which depends on claim 1, requires the immunomodulatory polynucleotide to comprise the sequence 5'-TCG-3'. Claim 26, which depends on claim 1, requires the immunomodulatory polynucleotide to comprise the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine-3'. Claims 27-30, which depends on claim 26, requires the immunomodulatory polynucleotide to comprise the sequence 5'-AACGTT -3'; 5'-purine, purine, C,G, pyrimidine, pyrimidine,C,C-3'; 5'-

[3] Chu et al. CpG Oligonucleotides act as adjuvants that switch on T helper 1 (Th1) immunity. J. Exp.

purine, purine, C,G, pyrimidine, pyrimidine,C,G-3'; and those selected from the group consisting of AACGTTCC, AACGTTCG, GACGTTCC AND GACGTTCG, respectively. Claim 31, which depends on claim 29, requires the immunomodulatory polynucleotide to comprise the sequence of SEQ ID NO: 1, which is TGACTGTGAACGTTCGAGATGA. Claim 32, which depends on claim 1, limits the individual to a mammal. Claim 33, which depends on claim 32, limits the mammal to a human.

Claim 37 is directed to the composition recited in claim 14, and requires the second antigen to be a viral variable polypeptide. Claims 40-41 are directed to the composition recited in claims 13 and 42, respectively.

Schwartz et al. teaches a complex comprising an immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3', the CpG motif, conjugated with an antigen, an allergen. [Lines 19-20, page 30; Lines 10-13 and Table 3, page 31; claims 25 and 27; and Figure 7, in particular.] The antigen that Schwartz et al. conjugated with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' to render a complex is AgE, also known as amb a1. In addition to the allergen antigen discussed above, Schwartz et al. also teaches antigens encompassing conserved and variable viral polypeptides and carrier molecules, and associating the antigen with carrier molecules. [Line 12, page 21 to line 2, page 22; and claims 43-44, in particular.]

The immunomodulatory polynucleotide of Schwartz et al. is SEQ ID NO: 2. This immunomodulatory polynucleotide of Schwartz et al. is the same as SEQ ID NO: 1

Med., November 17, 1997, Vol. 186, No. 10, 1623-1631.

recited in claim 31, which has the sequence TGACTGTGAACGTTCGAGATGA. The sequence TGACTGTGAACGTTCGAGATGA comprises the sequence 5'-TCG-3'; the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine-3'; the sequence 5'-AACGTT -3'; 5'-purine, purine, C,G, pyrimidine, pyrimidine,C,G-3'; and the sequence AACGTTCG. Schwartz et al. also teaches immunomodulatory polynucleotides comprising the following sequence: 5'-purine, purine, C,G, pyrimidine, pyrimidine,C,C-3', specifically AACGTTCC and GACGTTCC. Schwartz et al. teaches the single site administration of the complex to a mammal to induce an immune response in said mammal.

Schwartz et al. does not explicitly teach administering a second antigen with the complex. However, Schwartz et al. suggests that the immunomodulatory polynucleotide be administered with at least one, or more, antigens to modulate the immune response to the antigen. [Lines 9-15, page 12, in particular] The specific immune response that Schwartz et al. teaches is a Th1 immune response. Therefore, administering multiple antigens with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' would have been prima facie obvious to one of ordinary skill in the art, at the time the invention was made. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation for inducing a Th1 immune response to antigens administered with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' because Schwartz et al. teaches that the immunomodulatory polynucleotide is capable of inducing a Th1 immune response to antigens administered with the immunomodulatory polynucleotide.

This teaching is further evidenced by Chu et al. and Horner et al. Both Chu and Horner et al. teach the use of immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' as an adjuvant. [Figures 1 and 2 of Horner et al.; Results and Discussion sections of Chu et al.; and the Titles and Abstracts of both Chu and Horner et al., in particular.] Chu and Horner et al. teach the inherent ability of immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' to induce Th1 immune responses. Hence, the administration of a complex comprising immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' and at least one antigen would necessarily induce a Th1 immune response to all antigens. These facts would have rendered the instant claims prima facie obvious to one of ordinary skill in the art at the time the invention was made as no unexpected results have been demonstrated or noted in the instant specification.

2. Claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson et al.[4], as further evidenced by Horner et al. or Chu et al.

Carlson et al. teaches a complex comprising an immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3', the CpG motif, conjugated with an antigen, an allergen. [Figures 3-5, pages 36-37, and Line 22, page 19 and, in particular.] The antigen that Carlson et al. conjugated with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' to render a complex is AgE, also known as amb a1. In addition to the allergen antigen

[4] Carlson et al. WO 98/16247, published April 1998.

discussed above, Carlson et al. also teaches antigens encompassing conserved and variable viral polypeptides and carrier molecules, and associating the antigen with carrier molecules. [Pages 19-21 and 30-33, in particular.]

The immunomodulatory polynucleotide of Carlson et al. is TGACTGTGAACGTTCGAGATGA. [Page 36-37, in particular.] This immunomodulatory polynucleotide of Carlson et al. is the same as SEQ ID NO: 1 recited in claim 31. The sequence TGACTGTGAACGTTCGAGATGA comprises the sequence 5'-TCG-3'; the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine-3'; the sequence 5'-AACGTT -3'; 5'-purine, purine, C,G, pyrimidine, pyrimidine,C,G-3'; and the sequence AACGTTCG. Carlson et al. also teaches an immunomodulatory polynucleotides comprising the following sequence: 5'-purine, purine, C,G, pyrimidine, pyrimidine,C,C-3', specifically AACGTTCC and GACGTTCC. Carlson et al. teaches the single site administration of the complex to a mammal to induce an immune response in said mammal.

Carlson et al. does not explicitly teach administering a second antigen with the complex. However, Carlson et al. suggests that the immunomodulatory polynucleotide be administered with at least one, or more, antigens to modulate the immune response to the antigen. [Lines 5-10, page 17, in particular] The specific immune response that Carlson et al. teaches is a Th1 immune response. Therefore, administering multiple antigens with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' would have been prima facie obvious to one of ordinary skill in the art, at the time the invention was made. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation for inducing a Th1

immune response to antigens administered with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' because Carlson et al. teaches that the immunomodulatory polynucleotide is capable of inducing a Th1 immune response to antigens administered with the immunomodulatory polynucleotide.

This teaching is further evidenced by Chu et al. and Horner et al. Both Chu and Horner et al. teach the use of immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' as an adjuvant. [Figures 1 and 2 of Horner et al.; Results and Discussion sections of Chu et al.; and the Titles and Abstracts of both Chu and Horner et al., in particular.] Chu and Horner et al. teaches the inherent ability of immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' to induce Th1 immune responses. Hence, the administration of a complex comprising immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' and at least one antigen would necessarily induce a Th1 immune response to all antigens. These facts would have rendered the instant claims prima facie obvious to one of ordinary skill in the art at the time the invention was made as no unexpected results have been demonstrated or noted in the instant specification.

3. Claims 15 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Lee et al.[5]

[5] Lee et al. Control immune responses by gene immunization. Ann. Med., 1998; Vol. 30, 460-468.

Claim 15, which depends on claim 14, limits the conserved viral polypeptide to an influenza nucleocapsid protein. Claim 38, which depends on claim 37, also contain the same limitation as claim 15.

While Schwartz et al. teaches various antigens, Schwartz et al. does not teach influenza nucleocapsid protein. However, at the time the invention was made, Lee et al. teaches that this protein is the least affected by antibody-induced antigenic drift and studies using DNA encoding this protein have demonstrated protection. [Infectious Diseases, page 465, in particular.] Hence, one of ordinary skill in the art would have been motivated to incorporate a protein into a treatment composition that has already demonstrated protective properties in other studies. Furthermore, one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Schwartz et al. teaches compositions and methods involving a complex comprising immunostimulatory polynucleotide and polypeptide antigens to modulate the immune response to the antigen, and Lee et al. teaches subsequent Th1 responses upon administration of ISS with DNA encoded antigens. [Mechanism of action on pages 463-464, in particular.] Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art, at the time the invention was made, absent unexpected results.

4. Claims 15 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Lee et al.

Claim 15, which depends on claim 14, limits the conserved viral polypeptide to an influenza nucleocapsid protein. Claim 38, which depends on claim 37, also contain the same limitation as claim 15.

While Carlson et al. teaches various antigens, Carlson et al. does not teach influenza nucleocapsid protein. However, at the time the invention was made, Lee et al. teaches that this protein is the least affected by antibody-induced antigenic drift and studies using DNA encoding this protein have demonstrated protection. [Infectious Diseases, page 465, in particular.] Hence, one of ordinary skill in the art would have been motivated to incorporate a protein into a treatment composition that has already demonstrated protective properties in other studies. Furthermore, one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Carlson et al. teaches compositions and methods involving a complex comprising immunostimulatory polynucleotide and polypeptide antigens to modulate the immune response to the antigen, and Lee et al. teaches subsequent Th1 responses upon administration of ISS with DNA encoded antigens. [Mechanism of action on pages 463-464, in particular.] Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art, at the time the invention was made, absent unexpected results.

5. Claims 16 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Durali et al.[6]

Claim 16, which depends on claim 14, limits the conserved viral polypeptide to a human immunodeficiency virus (HIV) gag protein. Claim 39, which depends on claim 37, also contain the same limitation as claim 16.

While Schwartz et al. teaches various antigens, Schwartz et al. does not teach a human immunodeficiency virus (HIV) gag protein. However, at the time the invention was made, Durali et al. teaches that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV. [Abstract, in particular.] Since high variability in HIV is a major obstacle in selecting an antigen for a vaccine candidate and Durali et al. have been able to identify a conserved protein, one of ordinary skill in the art, at the time the invention was made, would have been motivated to incorporate this protein into a treatment composition. Furthermore, the skilled artisan would have had a reasonable expectation of success for producing the claimed invention because Schwartz et al. teaches that a wide variety of antigens can be used in the complex and method taught.

6. Claims 16 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Durali et al.

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[6] Durali et al. Cross reactions between the cytotoxic T-lymphocyte responses of human immunodeficiency virus-infected African and European patients. Journal of Virology, May 1998, Vol. 72, No. 5, 3547-3553.

Claim 16, which depends on claim 14, limits the conserved viral polypeptide to a human immunodeficiency virus (HIV) gag protein. Claim 39, which depends on claim 37, also contain the same limitation as claim 16.

While Carlson et al. teaches various antigens, Carlson et al. does not teach a human immunodeficiency virus (HIV) gag protein. However, at the time the invention was made, Durali et al. teaches that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV. [Abstract, in particular.] Since high variability in HIV is a major obstacle in selecting an antigen for a vaccine candidate and Durali et al. have been able to identify a conserved protein, one of ordinary skill in the art, at the time the invention was made, would have been motivated to incorporate this protein into a treatment composition. Furthermore, the skilled artisan would have had a reasonable expectation of success for producing the claimed invention because Carlson et al. teaches that a wide variety of antigens can be used in the complex and method taught.

7. Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Anderson et al.[7]

Claims 18-19, which depend on claim 17, limits the carrier molecule to diphtheria toxin mutant (CRM 197) and diphtheria toxoid, respectively.

While Schwartz et al. teaches various antigens, Schwartz et al. does not teach diphtheria toxin mutant (CRM 197) and diphtheria toxoid. However, at the time the

[7] Anderson et al. U.S. Patent No. 4673574, published June 1986.

invention was made, Anderson et al. teaches diphtheria toxin mutant (CRM 197) or diphtheria toxoid can be used as carriers in a vaccine preparation. [Lines 35-68, column 4; and Example 8, cited at line 9, column 14 through line 44, column 16, in particular.] Hence, one of ordinary skill in the art, at the time the invention was made, would have been motivated to use diphtheria toxin mutant (CRM 197) and diphtheria toxoid of Anderson in the method and composition taught by Schwartz et al. when administering the composition to children or immunocompromised individuals because the diphtheria toxins aid in eliciting a protective immune response, have no toxicity, and can be administered safely to children. [Lines 10-19, column 5; Table 7, column 14, in particular.] One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Schwartz et al. teaches that the complex comprising the immunostimulatory polynucleotide and an antigen can be combined with any known vaccine component, and diphtheria toxin mutant (CRM 197) and diphtheria toxoid taught by Anderson et al. are well known.

8. Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Anderson et al.

While Carlson et al. teaches various antigens, Carlson et al. does not teach diphtheria toxin mutant (CRM 197) and diphtheria toxoid. However, at the time the invention was made, Anderson et al. teaches diphtheria toxin mutant (CRM 197) or diphtheria toxoid can be used as carriers in a vaccine preparation. [Lines 35-68, column

4; and Example 8, cited at line 9, column 14 through line 44, column 16, in particular.] Hence, one of ordinary skill in the art, at the time the invention was made, would have been motivated to use diphtheria toxin mutant (CRM 197) and diphtheria toxoid of Anderson in the method and composition taught by Carlson et al. when administering the composition to children or immunocompromised individuals because the diphtheria toxins aid in eliciting a protective immune response, have no toxicity, and can be administered safely to children. [Lines 10-19, column 5; Table 7, column 14, in particular.] One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Carlson et al. teaches that the complex comprising the immunostimulatory polynucleotide and an antigen can be combined with any known vaccine component, and diphtheria toxin mutant (CRM 197) and diphtheria toxoid taught by Anderson et al. are well known.

(10) Response to Argument

9. In response to the rejection of claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42, under 35 U.S.C. 103(a), as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., Appellant submits that "Schwartz et al. does not teach all the elements of the claimed invention." [First paragraph under item I, page 25 of Brief, in particular.] Appellant submits that Schwartz et al. teaches a complex comprising an immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' conjugated with an antigen, but "does not teach administration of or modulation of an immune response to a second antigen."

This submission has been considered, however, it is not persuasive. Appellant is reminded that this is an obviousness rejection. Had Schwartz et al. taught all the elements of the claimed invention, the instant rejection would have been an anticipatory rejection under 35 U.S.C. § 102. Additionally, as presented in this Examiner's Answer and the previous office action that although Schwartz et al. does not explicitly teach administering a second antigen with the complex; Schwartz et al. suggests that the immunomodulatory polynucleotide be administered with at least one, or more, antigen to modulate the immune response to the antigen. [Lines 9-15, page 12, in particular] This suggestion clearly embraces the administration of a complex comprising immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' conjugated with at least one, one or more, antigen. It should be noted that the entire disclosure of Schwartz et al. is directed at the administration of immunomodulatory polynucleotides comprising the sequence 5'-cytosine,guanine-3' to modulate the immune responses, specifically Th1 immune response. Schwartz et al. also teaches the administration of the immunomodulatory polynucleotides with antigens to modulate the Th1 immune response to the antigen. In the instant case, the ability to modulate Th1 immune response is directed by the immunomodulatory polynucleotides. Hence, the immunomodulatory polynucleotides would have inherently immunomodulate the Th1 immune response to all antigens administered with it. Thus, a Th1 immune response to the second or subsequent antigens would necessarily be induced when administered with the immunomodulatory polynucleotides.

In response to the rejection, Appellant also criticizes the Office for taking contradictory position regarding the disclosure of Schwartz et al. Specifically, in the last 2 paragraph, page 25 of the brief, Appellant submits that the statements "[t]herefore, Schwartz et al. do[es] suggest the instant composition claimed" and "Schwartz does not teach administering a second antigen with the compositions".

The above submission has been considered, however, contrary to Appellant's assertion, the statements are not contradictory of one another. The first statement provides that Schwartz et al. suggests the claimed invention. This statement sets forth a suggestion that renders the claimed invention obvious. Whereas, the second statement sets forth that Schwartz et al. does not anticipate the claimed invention because Schwartz et al. does not teach a single embodiment that embraces all the limitations of the claimed invention.

In addition to above, it is noted that Appellant is taking issues with the Office's characterization of the disclosure made by Schwartz et al, particularly those provided at lines 29-31, page 12 of Schwartz et al. Appellant submits that contrary to the Office's position, the cited passage discloses administration of a complex comprising an immunomodulatory polynucleotide conjugated and an antigen in the form of a conjugate **OR** in the form of an admixture. Appellant submits that the cited passage does not disclose administration of a second antigen in conjunction with the complex, as claimed.

Appellant's submission has been considered, however, it is not found persuasive. It appears that Appellant has selectively misconstrued the teachings of Schwartz et al. In the instant case, as readily and clearly presented herein and the previous office

actions, Schwartz et al. clearly suggest the administration of a complex comprising the immunomodulatory polynucleotide and at least one, which is one or more, antigens. [Lines 9-15, page 12, in particular.] In addition to this suggestion, Schwartz et al. further notes that the immunomodulatory polynucleotide and the antigen can be administered in the form of a conjugate or co-administered in an admixture to modulate an immune response. [Lines 29-31, page 12, in particular.] Taking the suggestion with this teaching, it would have been prima facie obvious for one of ordinary skill to administer the complex of Schwartz et al. with more than one antigen, wherein the additional antigens can also be conjugated or admix with the immunomodulatory polynucleotide.

Appellant is also reminded that the rejection is based on the entire disclosure of Schwartz et al., and not just selective passages. The suggestion to administer a second antigen is clearly envisioned, though not explicit taught, by Schwartz et al. when Schwartz et al. suggests the administration of one or more antigens, conjugated or admixed with immunomodulatory polynucleotides.

It is further noted that Appellant has taken issues with the teachings of Horner et al. and Chu et al. Appellant submits that neither of the references cures the deficiencies of Schwartz et al.

Appellant's submission has been considered, however, it is not found persuasive. The instant obviousness rejection does not rely on the teachings of Horner et al. nor Chu et al. to compensate for any deficiency of Schwartz et al. The disclosure of Schwartz et al. is clearly enabled to compensate and cure the deficiencies noted in its working embodiments. Both Horner and Chu et al. are cited to further evidence the

ability of immunomodulatory polynucleotides comprising the sequence 5'-cytosine,guanine-3' to modulate the Th1 immune response to an antigen. As noted in the rejection, the rejection is based on Schwartz et al., as "evidenced by" Horner and Chu et al.

Appellant additionally submits that there is not motivation to modify the teaching of Schwartz et al.

Appellant's submission has been considered, however, it is not found persuasive. In the instant case, Schwartz et al. suggests the claimed invention when he discloses that at least one, one or more, antigens can be administered with the immunomodulatory polynucleotide. Schwartz et al. has demonstrated via his working embodiments that the immunomodulatory polynucleotide is capable of inducing a Th1 immune response to the antigen. Hence, the motivation here is the induction of Th1 immune response to antigens.

Appellant also submits that there is no reasonable expectation of success. Appellant submits that while one of ordinary skill in the art would expect an enhance immune response to an antigen when it is administered to an immunomodulatory polynucleotide, one of ordinary skill in the art, would not predict that an immune response to an second, unconjugated antigen would be modulated. To further support Appellant's position, Appellant submits that the Van Nest declaration.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's assertion, there is no reason to believe that anything but a reasonable expectation of success exists in rendering the claimed invention obvious. In

the instant case, the clear difference between the working embodiments of Schwartz et al. and the claimed invention is that the working embodiment of Schwartz et al., which induces an immune response, does not include the administration of a second antigen. However, at lines 9-15, page 12 of the disclosure of Schwartz et al., Schwartz et al. clearly suggests modifying the working embodiments with additional antigens. Furthermore, Schwartz et al. attributed the immune response, specifically Th1 immune response, induced to immunomodulatory polynucleotide. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Schwartz et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens, as taught by Schwartz et al., particularly since Schwartz et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 5-6, page 7, in particular.]

While Appellant may allege that that one of ordinary skill in the art would not predict that an immune response to a second, unconjugated antigen would be modulated, Appellant is reminded that in the absence of evidence, the allegation has no

significance. Appellant has yet to show any evidence demonstrating why one of ordinary skill in the art would not predict that an immune response to a second antigen would be modulated. Furthermore, Appellant is reminded that the threshold here is a "reasonable expectation of success" rather than absolute certainty of success as implied by Appellant's submission. Moreover, it should be noted that the claims do not require the second antigen to be unconjugated, as alleged by Appellant. As noted in the preceding paragraph, Schwartz et al. teaches taking advantage of the ability of immunomodulatory polynucleotides to modulate the immune response and use the immunomodulatory polynucleotide as an adjuvant to enhance the immune response to antigens, which Schwartz et al. has demonstrated in his working embodiments. Thus, in the instant case, any one of ordinary skill in the art, based on the teachings of Schwartz et al., would reasonably expect the induction of the immune response observed when an antigen is administered with the immunomodulatory polynucleotide to also apply to the second and subsequent antigens.

Regarding the Van Nest declaration, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the nature of the fact sought to be

established is whether one of ordinary skill would reasonably expect success in inducing a Th1 immune response to the second antigen when the second antigen is administered with a first antigen and an immunostimulatory oligonucleotide, the complex of Carlson et al. Appellant asserts that one of ordinary skill in the art would not be able to predict that the induction of a Th1 immune response noted for the antigen administered with the immunostimulatory oligonucleotide would also apply to the second antigen, when administered with the first antigen and the immunostimulatory oligonucleotide. Appellant submits Van Nest, an inventor for the claimed invention, declaration to evidence unexpected results. The declaration evidences the induction of a Th1 immune response to a second antigen. However, the declaration does not contain any evidence of unexpected results, as alleged by Appellant. In the instant case, the induction of a Th1 immune response to antigens administered with immunostimulatory oligonucleotides are expected to occur because Schwartz, Carlson, Horner and Chu et al. teaches the use of immunostimulatory oligonucleotide to induce a Th1 biased immune response. Hence, while Appellant is asserting unexpected results, it is found that there is nothing unexpected about the administration of a second antigen with an immunostimulatory oligonucleotide conjugated with an antigen. The administration of antigens subsequent to the first antigen with the immunostimulatory oligonucleotide should not and would not change the ability of the immunostimulatory oligonucleotide to modulate the immune response toward a Th1 biased response.

Appellant also submits that the Office failed to discuss the limitations of claims 14, 17 and 20, in any of the office actions mailed.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's position, the limitations of claims 14, 17 and 20 were discussed at page 5 of the very first office action, mailed July 30, 2001. At the cited passage, the Office note that Schwartz et al. teaches the limitations of these claims, and has cited line 13, page 21 to line 6 of page 24. At the cited passage, Schwartz et al. teaches antigens that encompasses conserved and variable viral polypeptides and carrier molecules.

Similar to the arguments presented above, Appellant also submits that the Office failed to discuss the limitations of claims 21-23, which require the induction of a Th1 immune response to the second antigen, induction of antigen-specific Th-1 associated antibodies be stimulated to the second antigen, and that interferon-gamma production be stimulated, respectively.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's position, the limitation of claim 21 was discussed at page 5 of the very first office action, mailed July 30, 2001. At the cited passage, the Office note that Schwartz et al. teaches the limitation of the claim, and has cited pages 27 through page 32 and claims 46-50 of Schwartz et al. At the cited passage, Schwartz et al. teaches the induction of a Th1 immune response to the antigen when administered with an immunomodulatory polynucleotide, and Schwartz et al. clarifies that the Th1 immune response induced includes the production of an antigen-specific Th1 associated antibodies. Specifically, lines 13-16, page 31, Schwartz et al. teaches the production of antigen-specific Th1 associated antibodies with the administration of a complex

comprising the immunostimulatory polynucleotide conjugated with an antigen. In the instant case, as discussed in the preceding paragraphs, the clear difference between the working embodiments of Schwartz et al. and the claimed invention is that the working embodiment of Schwartz et al., which induces the production of antigen-specific Th1 associated antibodies, does not include the administration of a second antigen. However, at lines 9-15, page 12 of the disclosure of Schwartz et al., Schwartz et al. clearly suggests modifying the working embodiments with additional antigens. Furthermore, Schwartz et al. attributed the immune response, specifically Th1 immune response, including the production of antigen-specific Th1 associated antibodies, induced to immunomodulatory polynucleotide. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Schwartz et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response, including the production of antigen-specific Th1 associated antibodies, would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens, as taught by Schwartz et al., particularly since Schwartz et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 5-6,

page 7, in particular.] In summation, Schwartz et al. teaches taking advantage of the ability of immunomodulatory polynucleotides to modulate the immune response and use the immunomodulatory polynucleotide as an adjuvant to enhance the immune response to antigens, which Schwartz et al. has demonstrated in his working embodiments. Thus, in the instant case, any one of ordinary skill in the art, based on the teachings of Schwartz et al., would reasonably expect the induction of the immune response observed when an antigen is administered with the immunomodulatory polynucleotide to also apply to the second and subsequent antigens. Additionally, regarding Appellant's assertion about the production of interferon-gamma, it should be noted that the production of interferon-gamma is in intrinsic property of a Th1 immune response. This is further evidenced by lines 26-27, page 1 of Schwartz et al, where Schwartz et al. clearly identifies interferon-gamma as a subset of Th1 immune response. Schwartz et al. also demonstrates that the Th1 immune response modulated by the immunomodulatory polynucleotides also include the production of interferon gamma, as shown in Figure 1.

Appellant also submits that the Office failed to discuss the limitations of claim 37 in any of the office actions mailed.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's position, the limitation of claim 37 was discussed at page 9 of the very first office action, mailed July 30, 2001. At the cited passage, the Office noted that although the reference does not specifically teach administering a conservative and a variable polypeptide, as the antigens, one of ordinary skill in the art at the time the

invention was made, would have been motivated to use this combination to cover a broader scope of variants in pathogens that may be encountered in the environment. From the reference, it is determined that the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

10. In response to the rejection of claims 15 and 38 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Lee et al., Appellant submits that Schwartz et al. in view of Lee et al. does not teach the claimed invention. Appellant primarily takes issue with the teachings of Schwartz et al., wherein Appellant submits that Schwartz et al. does not teach the administration of a second antigen and inducing an immune response to the second antigen. Appellant also submits that there is no reasonable expectation of success.

Appellant's submission has been considered. The significance of Schwartz et al. has been discussed in the preceding paragraph(s), hence, the discussion will not be repeated here. To summarize Schwartz et al., via his working embodiments, Schwartz et al. teaches the induction of an immune response to an antigen when the antigen is administered as a complex with an immunostimulatory polynucleotide. While the working embodiment of Schwartz et al. does not include the administration of a second antigen, Schwartz et al. suggests the administration of an immunomodulatory polynucleotide with one or more antigens, wherein the immunomodulatory polynucleotides can be conjugated or admixed with the antigen. Furthermore, Schwartz

et al. attributed the immune response. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Schwartz et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens, as taught by Schwartz et al., particularly since Schwartz et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 5-6, page 7, in particular.]

As discussed in the rejection, Schwartz et al. does not teach influenza nucleocapsid protein. However, at the time the invention was made, Lee et al. teaches that this protein is the least affected by antibody-induced antigenic drift and studies using DNA encoding this protein have demonstrated protection. [Infectious Diseases, page 465, in particular.] Hence, one of ordinary skill in the art would have been motivated to incorporate a protein into a treatment composition that has already demonstrated protective properties in other studies. Furthermore, one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Schwartz et al. teaches compositions and methods involving a complex comprising immunostimulatory polynucleotide and

polypeptide antigens to modulate the immune response to the antigen, and Lee et al. teaches subsequent Th1 responses upon administration of ISS with DNA encoded antigens. [Mechanism of action on pages 463-464, in particular.] Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art, at the time the invention was made, absent unexpected results.

11. In response to the rejection of claims 16 and 39 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Durali et al. Appellant submits that Schwartz et al. in view of Durali et al. does not teach the claimed invention. Appellant primarily takes issue with the teachings of Schwartz et al., wherein Appellant submits that Schwartz et al. does not teach the administration of a second antigen and inducing an immune response to the second antigen. Appellant also submits that there is no reasonable expectation of success.

Appellant's submission has been considered. The significance of Schwartz et al. has been discussed in the preceding paragraph(s), hence, the discussion will not be repeated here. To summarize Schwartz et al., via his working embodiments, Schwartz et al. teaches the induction of an immune response to an antigen when the antigen is administered as a complex with an immunostimulatory polynucleotide. While the working embodiment of Schwartz et al. does not include the administration of a second antigen, Schwartz et al. suggests the administration of an immunomodulatory polynucleotide with one or more antigens, wherein the immunomodulatory polynucleotides can be conjugated or admixed with the antigen. Furthermore, Schwartz

et al. attributed the immune response. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Schwartz et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens as taught by Schwartz et al., particularly since Schwartz et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 5-6, page 7, in particular.]

As discussed in the rejection, while Schwartz et al. teaches various antigens, Schwartz et al. does not teach a human immunodeficiency virus (HIV) gag protein. However, at the time the invention was made, Durali et al. teaches that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV. [Abstract, in particular.] Since high variability in HIV is a major obstacle in selecting an antigen for a vaccine candidate and Durali et al. have been able to identify a conserved protein, one of ordinary skill in the art, at the time the invention was made, would have been motivated to incorporate this protein into a treatment composition. Furthermore, the skilled artisan would have had a reasonable expectation of success for producing

the claimed invention because Schwartz et al. teaches that a wide variety of antigens can be used in the complex and method taught.

12. In response to the rejection of claims 18-19 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Anderson et al. Appellant submits that Schwartz et al. in view of Anderson et al. does not teach the claimed invention. Appellant primarily takes issue with the teachings of Schwartz et al., wherein Appellant submits that Schwartz et al. does not teach the administration of a second antigen and inducing an immune response to the second antigen. Appellant also submits that there is no reasonable expectation of success.

Appellant's submission has been considered. The significance of Schwartz et al. has been discussed in the preceding paragraph, hence, the discussion will not be repeated here. To summarize Schwartz et al., via his working embodiments, Schwartz et al. teaches the induction of an immune response to an antigen when the antigen is administered as a complex with an immunostimulatory polynucleotide. While the working embodiment of Schwartz et al. does not include the administration of a second antigen, Schwartz et al. suggests the administration of an immunomodulatory polynucleotide with one or more antigens, wherein the immunomodulatory polynucleotides can be conjugated or admixed with the antigen. Furthermore, Schwartz et al. attributed the immune response. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced

by immunomodulatory polynucleotides, especially since Schwartz et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens as taught by Schwartz et al., particularly since Schwartz et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 5-6, page 7, in particular.]

As discussed in the rejection, while Schwartz et al. teaches various antigens, Schwartz et al. does not teach diphtheria toxin mutant (CRM 197) and diphtheria toxoid. However, at the time the invention was made, Anderson et al. teaches diphtheria toxin mutant (CRM 197) or diphtheria toxoid can be used as carriers in a vaccine preparation. [Lines 35-68, column 4; and Example 8, cited at line 9, column 14 through line 44, column 16, in particular.] Hence, one of ordinary skill in the art, at the time the invention was made, would have been motivated to use diphtheria toxin mutant (CRM 197) and diphtheria toxoid of Anderson in the method and composition taught by Schwartz et al. when administering the composition to children or immunocompromised individuals because the diphtheria toxins aid in eliciting a protective immune response, have no toxicity, and can be administered safely to children. [Lines 10-19, column 5; Table 7, column 14, in particular.] One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention

because Schwartz et al. teaches that the complex comprising the immunostimulatory polynucleotide and an antigen can be combined with any known vaccine component, and diphtheria toxin mutant (CRM 197) and diphtheria toxoid taught by Anderson et al. are well known.

13. In response to the rejection of claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42, under 35 U.S.C. 103(a), as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., Appellant submits that "Carlson et al. does not teach all the elements of the claimed invention." [First paragraph under item I, page 25 of Brief, in particular.] Appellant submits that Carlson et al. teaches a complex comprising an immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' conjugated with an antigen, but "does not teach administration of or modulation of an immune response to a second antigen."

This submission has been considered, however, it is not persuasive. Appellant is reminded that this is an obviousness rejection. Had Carlson et al. teaches all the elements of the claimed invention, the instant rejection would have been an anticipatory, under 35 U.S.C. § 102, rejection. Additionally, as presented in this Examiner's Answer and the previous office action that although Carlson et al. does not explicitly teach administering a second antigen with the complex; Carlson et al. suggests that the immunomodulatory polynucleotide be administered with at least one, one or more, antigen to modulate the immune response to the antigen. [Lines 5-10, page 17, in particular] At the cited passage, Carlson et al. teaches that the oligonucleotide base of the ISS-PN/IMM, which is the ISS-PN portion, is conjugated to an IMM which includes

an antigen. Continuing with the same passage, Carlson et al. then notes that the conjugated ISS-PN and IMM that includes antigens, rendering ISS-PN/IMM may further include an immunomodulatory agent. Carlson et al. defines "immunomodulatory agent" to include antigen. [Lines 2-3, page 18, in particular.] Thus, the cited passage evidences that Carlson et al. teaches an ISS-PN/IMM with an immunomodulatory agent, wherein the ISS-PN of Carlson et al. is an immunostimulatory polynucleotide, IMM is the antigen, and the immunostimulatory agent is another antigen. Hence, Carlson et al. clearly embraces a second antigen with the complex comprising an immunostimulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' conjugated to an antigen. It should be noted that the claims recite the term "comprising" and do not require the "second antigen" to be an entity that is independent from the complex comprising immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' conjugated antigen. Furthermore, it should be noted that the entire disclosure of Carlson et al. is directed at the administration of immunomodulatory polynucleotides comprising the sequence 5'-cytosine,guanine-3' to modulate the immune responses, specifically Th1 immune response. Carlson et al. also teaches the administration of the immunomodulatory polynucleotides with antigens to modulate the Th1 immune response to the antigen. In the instant case, the ability to modulate Th1 immune response is directed by the immunomodulatory polynucleotides. Hence, the immunomodulatory polynucleotides would have inherently immunomodulate the Th1 immune response to all antigens administered with it. Thus, a Th1 immune response to

the second or subsequent antigens would necessarily be induced when administered with the immunomodulatory polynucleotides.

It is further noted that Appellant has taken issues with the teachings of Horner et al. and Chu et al. Appellant submits that neither of the references cures the deficiencies of Carlson et al.

Appellant's submission has been considered, however, it is not found persuasive. The instant obviousness rejection does not rely on the teachings of Horner et al. nor Chu et al. to compensate for any deficiency of Carlson et al. The disclosure of Carlson et al. is clearly enabled to compensate and cure the deficiencies noted in its working embodiments. Both Horner and Chu et al. are cited to further evidence the ability of immunomodulatory polynucleotides comprising the sequence 5'-cytosine,guanine-3' to modulate the Th1 immune response to an antigen. As noted in the rejection, the rejection is based on Carlson et al., as "evidenced by" Horner and Chu et al.

Appellant additionally submits that there is not motivation to modify the teaching of Carlson et al.

Appellant's submission has been considered, however, it is not found persuasive. In the instant case, Carlson et al. suggests the claimed invention when he discloses that more than one antigen can be administered with the immunomodulatory polynucleotide. Carlson et al. has demonstrated via his working embodiments that the immunomodulatory polynucleotide is capable of inducing a Th1 immune response to the antigen. Hence, the motivation here is the induction of Th1 immune response to antigens.

Appellant also submits that there is no reasonable expectation of success. Appellant submits that while one of ordinary skill in the art would expect an enhance immune response to an antigen when it is administered to an immunomodulatory polynucleotide, one of ordinary skill in the art, would not predict that an immune response to an second, unconjugated antigen would be modulated. To further support Appellant's position, Appellant submits that the Van Nest declaration.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's assertion, there is no reason to believe that anything but a reasonable expectation of success exists in rendering the claimed invention obvious. In the instant case, the clear difference between the working embodiments of Carlson et al. and the claimed invention is that the working embodiment of Carlson et al., which induces an immune response, does not include the administration of a second antigen. However, at lines 5-10, page 17 of the disclosure of Carlson et al., Carlson et al. clearly suggests modifying the working embodiments with additional antigens. Furthermore, Carlson et al. attributed the immune response, specifically Th1 immune response, induced to immunomodulatory polynucleotide. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Carlson et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in

the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens as taught by Carlson et al., particularly since Carlson et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 7-13, page 3, in particular.]

While Appellant may allege that that one of ordinary skill in the art would not predict that an immune response to a second, unconjugated antigen would be modulated, Appellant is reminded that in the absence of evidence, the allegation has no significance. Appellant has yet to show any evidence demonstrating why one of ordinary skill in the art would not predict that an immune response to a second antigen would be modulated. Furthermore, Appellant is reminded that the threshold here is a "reasonable expectation of success" rather than absolute expectation of success as implied by Appellant's submission. Moreover, it should be noted that the claims do not require the second antigen to be unconjugated, as alleged by Appellant. As noted in the preceding paragraph, Carlson et al. teaches taking advantage of the ability of immunomodulatory polynucleotides to modulate the immune response and use the immunomodulatory polynucleotide as an adjuvant to enhance the immune response to antigens, which Carlson et al. has demonstrated in his working embodiments. Thus, in the instant case, any one of ordinary skill in the art, based on the teachings of Carlson et al., would reasonably expect the induction of the immune response observed when an antigen is

administered with the immunomodulatory polynucleotide to also apply to the second and subsequent antigens.

Regarding the Van Nest declaration, In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the nature of the fact sought to be established is whether one of ordinary skill would reasonably expect success in inducing a Th1 immune response to the second antigen when the second antigen is administered with a first antigen and an immunostimulatory oligonucleotide, the complex of Carlson et al. Appellant asserts that one of ordinary skill in the art would not be able to predict that the induction of a Th1 immune response noted for the antigen administered with the immunostimulatory oligonucleotide would also apply to the second antigen, when administered with the first antigen and the immunostimulatory oligonucleotide. Appellant submits Van Nest, an inventor for the claimed invention, declaration to evidence unexpected results. The declaration evidences the induction of a Th1 immune response to a second antigen. However, the declaration does not contain any evidence of unexpected results, as alleged by Appellant. In the instant case, the induction of a Th1 immune response to antigens administered with

immunostimulatory oligonucleotides are expected to occur because Schwartz, Carlson, Horner and Chu et al. teaches the use of immunostimulatory oligonucleotide to induce a Th1 biased immune response. Hence, while Appellant is asserting unexpected results, it is found that there is nothing unexpected about the administration of a second antigen with an immunostimulatory oligonucleotide conjugated with an antigen. The administration of antigens subsequent to the first antigen with the immunostimulatory oligonucleotide should not and would not change the ability of the immunostimulatory oligonucleotide to modulate the immune response toward a Th1 biased response.

Appellant also submits that the Office failed to discuss the limitations of claims 14, 17 and 20, in any of the office actions mailed.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's position, the limitations of claims 14, 17 and 20 were discussed at pages 5-6 of the very first office action, mailed July 30, 2001. At the cited passage, the Office note that Carlson et al. teaches the limitations of these claims, and has cited pages 10-33, which includes pages 19-21. At the cited passage, Carlson et al. teaches antigens that encompasses conserved and variable viral polypeptides and carrier molecules.

Similar to the arguments presented above, Appellant also submits that the Office failed to discuss the limitations of claims 21-23, which require the induction of a Th1 immune response to the second antigen, induction of antigen-specific Th-1 associated antibodies be stimulated to the second antigen, and that interferon-gamma production be stimulated, respectively.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's position, the limitation of claim 21 was discussed at pages 5-6 of the very first office action, mailed July 30, 2001. At the cited passage, the Office note that Carlson et al. teaches the limitation of the claim, and has cited pages 35-39 and claims 54-111 of Carlson et al. At the cited passage, Carlson et al. teaches the induction of a Th1 immune response to the antigen when administered with an immunomodulatory polynucleotide, and Carlson et al. clarifies that the Th1 immune response induced includes the production of an antigen-specific Th1 associated antibodies. Specifically, at pages 35-39, Carlson et al. teaches the production of antigen-specific Th1 associated antibodies with the administration of a complex comprising the immunostimulatory polynucleotide conjugated with an antigen. In the instant case, as discussed in the preceding paragraphs, the clear difference between the working embodiments of Carlson et al. and the claimed invention is that the working embodiment of Carlson et al., which induces the production of antigen-specific Th1 associated antibodies, does not include the administration of a second antigen. However, at lines 5-10, page 17 of the disclosure of Carlson et al., Carlson et al. clearly suggests modifying the working embodiments with additional antigens. Furthermore, Carlson et al. attributed the immune response, specifically Th1 immune response, including the production of antigen-specific Th1 associated antibodies, induced to immunomodulatory polynucleotide. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced

by immunomodulatory polynucleotides, especially since Carlson et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response, including the production of antigen-specific Th1 associated antibodies, would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens as taught by Carlson et al., particularly since Carlson et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 7-13, page 3, in particular.] In summation, Carlson et al. teaches taking advantage of the ability of immunomodulatory polynucleotides to modulate the immune response and use the immunomodulatory polynucleotide as an adjuvant to enhance the immune response to antigens, which Carlson et al. has demonstrated in his working embodiments. Thus, in the instant case, any one of ordinary skill in the art, based on the teachings of Carlson et al., would reasonably expect the induction of the immune response observed when an antigen is administered with the immunomodulatory polynucleotide to also apply to the second and subsequent antigens. Additionally, regarding Appellant's assertion about the production of interferon-gamma, it should be noted that the production of interferon-gamma is in intrinsic property of a Th1 immune response. This is further evidenced by lines 3-4, page 4 of Carlson et al, where Carlson et al. clearly identifies interferon-gamma as a subset of Th1 immune response. Carlson et al. also demonstrates that the

Th1 immune response modulated by the immunomodulatory polynucleotides also include the production of interferon gamma, as shown in Figure 6.

Appellant also submits that the Office failed to discuss the limitations of claim 37 in any of the office actions mailed.

Appellant's submission has been considered, however, it is not found persuasive. Contrary to Appellant's position, the limitation of claim 37 was discussed at page 9 of the very first office action, mailed July 30, 2001. At the cited passage, the Office note that although the reference does not specifically teach administering a conservative and a variable polypeptide, as the antigens, however, one of ordinary skill in the art, at the time the invention was made, would have been motivated to use this combination to cover a broader scope of variants in pathogens that may be encountered in the environment. From the reference, it is determined that the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

14. In response to the rejection of claims 15 and 38 under 35 U.S.C. 103(a) as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Lee et al., Appellant submits that Carlson et al. in view of Lee et al. does not teach the claimed invention. Appellant primarily takes issue with the teachings of Carlson et al., wherein Appellant submits that Carlson et al. does not teach the administration of a second antigen and inducing an immune response to the second antigen. Appellant also submits that there is no reasonable expectation of success.

Appellant's submission has been considered. The significance of Carlson et al. has been discussed in the preceding paragraph(s), hence, the discussion will not be repeated here. To summarize Carlson et al., via his working embodiments, Carlson et al. teaches the induction of an immune response to an antigen when the antigen is administered as a complex with an immunostimulatory polynucleotide. While the working embodiment of Carlson et al. does not include the administration of a second antigen, Carlson et al. suggests the administration of an immunomodulatory polynucleotide with one or more antigens, wherein the immunomodulatory polynucleotides can be conjugated or admixed with the antigen. Furthermore, Carlson et al. attributed the immune response. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Carlson et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens, as taught by Carlson et al., particularly since Carlson et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 7-13, page 3, in particular.]

As discussed in the rejection, Carlson et al. does not teach influenza nucleocapsid protein. However, at the time the invention was made, Lee et al. teaches that this protein is the least affected by antibody-induced antigenic drift and studies using DNA encoding this protein have demonstrated protection. [Infectious Diseases, page 465, in particular.] Hence, one of ordinary skill in the art would have been motivated to incorporate a protein into a treatment composition that has already demonstrated protective properties in other studies. Furthermore, one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Carlson et al. teaches compositions and methods involving a complex comprising immunostimulatory polynucleotide and polypeptide antigens to modulate the immune response to the antigen, and Lee et al. teaches subsequent Th1 responses upon administration of ISS with DNA encoded antigens. [Mechanism of action on pages 463-464, in particular.] Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art, at the time the invention was made, absent unexpected results.

15. In response to the rejection of claims 16 and 39 under 35 U.S.C. 103(a) as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Durali et al. Appellant submits that Carlson et al. in view of Durali et al. does not teach the claimed invention. Appellant primarily takes issue with the teachings of Carlson et al., wherein Appellant submits that Carlson et al. does not teach the administration of a

second antigen and inducing an immune response to the second antigen. Appellant also submits that there is no reasonable expectation of success.

Appellant's submission has been considered. The significance of Carlson et al. has been discussed in the preceding paragraph(s), hence, the discussion will not be repeated here. To summarize Carlson et al., via his working embodiments, Carlson et al. teaches the induction of an immune response to an antigen when the antigen is administered as a complex with an immunostimulatory polynucleotide. While the working embodiment of Carlson et al. does not include the administration of a second antigen, Carlson et al. suggests the administration of an immunomodulatory polynucleotide with one or more antigens, wherein the immunomodulatory polynucleotides can be conjugated or admixed with the antigen. Furthermore, Carlson et al. attributed the immune response. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Carlson et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens, as taught by Carlson et al., particularly since Carlson et al. teaches taking

advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 7-13, page 3, in particular.]

As discussed in the rejection, while Carlson et al. teaches various antigens, Carlson et al. does not teach a human immunodeficiency virus (HIV) gag protein. However, at the time the invention was made, Durali et al. teaches that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV. [Abstract, in particular.] Since high variability in HIV is a major obstacle in selecting an antigen for a vaccine candidate and Durali et al. have been able to identify a conserved protein, one of ordinary skill in the art, at the time the invention was made, would have been motivated to incorporate this protein into a treatment composition. Furthermore, the skilled artisan would have had a reasonable expectation of success for producing the claimed invention because Carlson et al. teaches that a wide variety of antigens can be used in the complex and method taught.

16. In response to the rejection of claims 18-19 under 35 U.S.C. 103(a) as being unpatentable over Carlson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 13-14, 17, 20-23, 25-33, 37 and 40-42 above, in further view of Anderson et al. Appellant submits that Carlson et al. in view of Anderson et al. does not teach the claimed invention. Appellant primarily takes issue with the teachings of Carlson et al., wherein Appellant submits that Carlson et al. does not teach the administration of a second antigen and inducing an immune response to the second antigen. Appellant also submits that there is no reasonable expectation of success.

Appellant's submission has been considered. The significance of Carlson et al. has been discussed in the preceding paragraph(s), hence, the discussion will not be repeated here. To summarize Carlson et al., via his working embodiments, Carlson et al. teaches the induction of an immune response to an antigen when the antigen is administered as a complex with an immunostimulatory polynucleotide. While the working embodiment of Carlson et al. does not include the administration of a second antigen, Carlson et al. suggests the administration of an immunomodulatory polynucleotide with one or more antigens, wherein the immunomodulatory polynucleotides can be conjugated or admixed with the antigen. Furthermore, Carlson et al. attributed the immune response. Since the induction of a Th1 immune response is attributed to immunomodulatory polynucleotides, the administration of a second or subsequent antigen would not and should not affect the Th1 immune response induced by immunomodulatory polynucleotides, especially since Carlson et al. all ready teaches that conjugation of an antigen to the immunomodulatory polynucleotides does not affect or hinder the ability of the immunomodulatory polynucleotides to induce a Th1 immune response. Hence, it is reasonable to expect, in the absence of evidence to the contrary, that the induction of a Th1 immune response would also exist when a second or subsequent antigen is administered. The Th1 immune response will also be directed at the antigens, as taught by Carlson et al., particularly since Carlson et al. teaches taking advantage of this observed induction of Th1 immune response and use the immunomodulatory polynucleotide as an adjuvant. [Lines 7-13, page 3, in particular.]

As discussed in the rejection, while Carlson et al. teaches various antigens, Carlson et al. does not teach diphtheria toxin mutant (CRM 197) and diphtheria toxoid. However, at the time the invention was made, Anderson et al. teaches diphtheria toxin mutant (CRM 197) or diphtheria toxoid can be used as carriers in a vaccine preparation. [Lines 35-68, column 4; and Example 8, cited at line 9, column 14 through line 44, column 16, in particular.] Hence, one of ordinary skill in the art, at the time the invention was made, would have been motivated to use diphtheria toxin mutant (CRM 197) and diphtheria toxoid of Anderson in the method and composition taught by Carlson et al. when administering the composition to children or immunocompromised individuals because the diphtheria toxins aid in eliciting a protective immune response, have no toxicity, and can be administered safely to children. [Lines 10-19, column 5; Table 7, column 14, in particular.] One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation in producing the claimed invention because Carlson et al. teaches that the complex comprising the immunostimulatory polynucleotide and an antigen can be combined with any known vaccine component, and diphtheria toxin mutant (CRM 197) and diphtheria toxoid taught by Anderson et al. are well known.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Emily M. Le/
Patent Examiner
Art Unit 1648

Conferees:

/Bruce R. Campell/
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